

## REMARKS

Claims 1-7 and 10-21 are now in the application.

Claims 1-7 and 10-21 were rejected under 35 USC 103(a) as being unpatentable over GB 947643 to Merck et al. and applicants' acknowledged prior art in view of US Patent 4,061,660 to Kijima et al., US Patent 4,039,573 to Kijima et al. and US Patent 4,163,864 to Morita et al. The cited references fail to render obvious the present.

Before addressing the rejection over the cited art, a discussion of the present invention would be helpful. In particular, the present invention is directed to a process of purifying reduced coenzyme Q<sub>10</sub>. According to the present invention, a water-soluble organic solvent or a mixed solvent composed of a water-soluble organic solvent and water is used to wash crystals and/or oil of reduced coenzyme Q<sub>10</sub>, and a water-soluble impurity derived from the reducing agent such as hyposulfurous acid or ascorbic acids is thereby removed. A distinctive feature of the present invention is that a water-soluble organic solvent or a mixed solvent composed of a water-soluble organic solvent and water is used for washing. In order to remove impurities highly soluble in water such as hyposulfurous acid, ascorbic acids and derivatives thereof, those skilled in the art would use water for washing. However, as previously explained in prior responses, impurities cannot be sufficiently removed when water is used for washing crystals and/or oil of reduced coenzyme Q<sub>10</sub>. Those skilled in the art would not expect that water-soluble organic solvents are much more effective than water for removing water-soluble impurities.

Further, washing of the crystals and/or oil should be distinguished from washing of the solution. If a solution is washed with a washing solvent, it is necessary that the solution and the washing solvent are separable. However, depending on the reaction solvent used for the reduction of oxidized coenzyme Q<sub>10</sub>, it is impossible to wash the solution. For example, in Production Example 1 of the present application, oxidized coenzyme Q<sub>10</sub> is reduced in ethanol. It is impossible to wash the reaction solution containing ethanol without carrying out an additional process such as replacement of ethanol with another solvent.

Even if the solution and the washing solvent are separable, washing of the solution is not favorable in a large-scale production since a large quantity of washing solvent is required and also it is troublesome and difficult to separate a liquid phase from the other liquid phase after the washing process.

According to the present invention, washing can be carried out regardless of the reaction solution and also the washing solvent and the desired product can be easily separated since the crystals and/or oil are/is washed.

According to the Office Action, it is a common practice to use suitable solvents for washing/purifying the crystals.

With respect to the above comment, enclosed herewith are documents showing the solubility of L-ascorbic acid. In particular, please see the enclosed partial English translation of *Kagaku Binran* (Handbook of Chemistry) demonstrating that the solubility of L-ascorbic acid in water is 25 g/100 g H<sub>2</sub>O at 25°C<sup>1</sup>, while the solubility in ethanol is only 0.2 g/100 g EtOH at 25°C. In order to remove impurities so highly soluble in water, those skilled in the art would naturally think that water is a suitable solvent for washing. Further along these lines, attached is a Declaration under 37 CFR 1.132 by Takahiro Ueda, which verifies that the solubility of L-ascorbic acid in ethanol is 0.2 g/100 g EtOH at 25°C.

However, contrary to the above expectations, the impurities cannot be removed sufficiently when water is used for washing crystals and/or oil of reduced coenzyme Q<sub>10</sub>. Moreover, employing a water-soluble organic solvent would be counterintuitive.

Examples provided in the present specification demonstrate the unexpected results achievable by the present invention. For instance, in Example 1 of the present application, crystals of reduced coenzyme Q<sub>10</sub> (containing 3.2% of L-ascorbic acid and 0.36% of oxalic acid) obtained in Production Example 1 were washed with an aqueous ethanol solutions (mixtures of

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<sup>1</sup> As shown in Table 8.61 of *Kagaku Binran*, the solubility of L-ascorbic acid in water is 19.8 at 25°C. It is the mass of L-ascorbic acid in 100 g of the saturated solution. Namely 100 g of the saturated solution contains 19.8 g of L-ascorbic acid and 80.2 g of water, which equal to approximately 25 g of L-ascorbic acid in 100 g of water.

ethanol and water). As shown in Table 1, after washing, the contents of L-ascorbic acid were 0.07% or less and the contents of oxalic acid were 0.05% or less. In Example 2, crystals were washed with ethanol. After washing, the contents of L-ascorbic acid and oxalic acid were 0.06% and 0.07%, respectively. On the other hand, in Comparative Example 1 where water was used for washing, the content of L-ascorbic acid was 0.18% and the content of oxalic acid was 0.15%.

In Example 3, reduced coenzyme Q<sub>10</sub> in an oily form was washed with an aqueous ethanol solution. The contents of L-ascorbic acid and oxalic acid were 0.02% and 0.03%, respectively after washing. On the other hand, in Comparative Example 2 where water was used for washing, the content of L-ascorbic acid was as high as 0.43% and the content of oxalic acid was 0.19%.

It is unpredictable that impurities can be removed so efficiently when a water-soluble organic solvent or a mixed solvent composed of a water-soluble organic solvent and water is used.

GB 947643 fails to suggest the present invention since, among other things, as appreciated by the examiner, GB 947643 does not even imply washing of the crystals. Moreover, the product therein, as recognized by the examiner, would necessarily contain water-insoluble impurities such as the reducing agent and/or derivatives derived from the reducing agent. The secondary references do not overcome the deficiencies of GB 947643 with respect to rendering unpatentable the present invention.

The Office Action does not provide the adequate rationale or reasoning as to why persons skilled in the art would wash crystals and/or oil with a water-soluble organic solvent. As already discussed in previous responses, the secondary references do not teach washing crystals.

In Example 1 of US Patent 4,061,660 to Kijima et al, the reaction mixture contained silica-alumina (please see Col. 4, lines 40 to 43), and after filtration the silica-alumina was washed with diethyl ether to remove and collect a desired product which adhered to the

surface of silica-alumina. Accordingly, those skilled in the art would readily understand that the procedure of Kijima et al. does not include washing of crystals or oil of a desired product for removal of impurity.

In Example 3 of US Patent 4,039,573 to Kijima et al., the filtrate was washed with water and then with a weak-caustic soda aqueous solution. Namely, the reference teaches washing the solution of a desired product. The procedure does not include washing of crystals or oil of a desired product for removal of impurity as required by the present invention. It is respectfully requested that the location in Kijima et al. where washing of crystals is disclosed be specifically identified.

In Example 1 of US Patent 4,163,864 to Morita et al., the filtrate was washed with a methanolic aqueous sodium hydroxide solution and then with an aqueous methanol solution (please see col. 4, lines 31 to 36). Therefore, the reference teaches washing the filtrate liquor, namely a solution of a desired product. The procedure does not include a washing of crystals or oil of a desired product for removal of impurity as required by the present invention. It is respectfully requested that the location in Morita et al. where washing of crystals is disclosed be specifically identified.

Since the secondary references are silent about impurities derived from hyposulfurous acid, hyposulfurous acid salts, ascorbic acids, esters of ascorbic acids or salts of ascorbic acids and since they do not disclose washing crystals or oil, it is not at all apparent why the cited references would render obvious the present invention. The rejection relies upon impermissible "hindsight".

In the Office Action, the examiner commented concerning possible comparative experiments. However, since a *prima facie* case of obviousness has not even been established, such comparative experiments are not actually needed in this application. Please see *Takeda v. Alphapharm*, 492 F. 3<sup>rd</sup> 1350 (Fed. Cir. 2007). Nevertheless, as discussed above, the present application already includes comparative examples that illustrate the unexpected results obtained from the process of the present invention. Furthermore, please see the Declaration by Mr. Ueda

and the partial translation of *Kagaku Binran* (Handbook of Chemistry), which further support the non-obviousness of the present invention. Also, the prior art should be considered as a whole, and portions arguing against or teaching away from the claimed invention must be considered. See *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 230 U.S.P.Q. 46 (Fed. Cir. 1986).

Accordingly, the present invention is not rendered obvious GB 947643 to Merck et al. in view of US Patent 4,061,660 to Kijima et al., US Patent 4,039,573 to Kijima et al. and US Patent 4,163,864 to Morita et al.

The mere fact that the cited art may be modified in the manner suggested in the Office Action does not make this modification obvious, unless the cited art suggest the desirability of the modification or there is well reasoned and articulated rationale to do so. This is not present in the present record. The Examiner's attention is kindly directed to *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727; 82 USPQ2d 1385 (2007), *In re Lee* 61 USPQ2d 1430 (Fed. Cir. 2002), *In re Dembiczak et al.* 50 USPQ2d. 1614 (Fed. Cir. 1999), *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984), *In re Laskowski*, 10 USPQ2d. 1397 (Fed. Cir. 1989) and *In re Fritch*, 23, USPQ2d. 1780 (Fed. Cir. 1992).

Also, the cited art lacks the necessary direction or incentive to those of ordinary skill in the art to render a rejection under 35 USC 103 sustainable. The cited art fails to provide the degree of predictability of success of achieving the properties attainable by the present invention needed to sustain a rejection under 35 USC 103. See *KSR Int'l Co. v. Teleflex, Inc.* supra, *Diversitech Corp. v. Century Steps, Inc.* 7 USPQ2d 1315 (Fed. Cir. 1988), *In re Mercier*, 187 USPQ 774 (CCPA 1975) and *In re Naylor*, 152 USPQ 106 (CCPA 1966).

Moreover, the properties of the subject matter and improvements which are inherent in the claimed subject matter and disclosed in the specification are to be considered when evaluating the question of obviousness under 35 USC 103. See *KSR Int'l Co. v. Teleflex, Inc.*,

*Antonie*, 195, USPQ 6 (CCPA 1977), *In re Estes*, 164 USPQ 519 (CCPA 1970), and *In re Papesch*, 137 USPQ 43 (CCPA 1963).

No property can be ignored in determining patentability and comparing the claimed invention to the cited art. Along these lines, see *In re Papesch*, supra, *In re Burt et al*, 148 USPQ 548 (CCPA 1966), *In re Ward*, 141 USPQ 227 (CCPA 1964), and *In re Cescon*, 177 USPQ 264 (CCPA 1973).

In view of the above, consideration and allowance are respectfully solicited.

In the event the Examiner believes an interview might serve in any way to advance the prosecution of this application, the undersigned is available at the telephone number noted below.

The Office is authorized to charge any necessary fees to Deposit Account No. 22-0185, under Order No. 21581-00496-US from which the undersigned is authorized to draw.

Dated: April 22, 2010

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Takahiro Ueda et al.

Serial No.: 10/541,446

Art Unit: 1621

Filed : June 22, 2006

Examiner: KATAKAM, SUDHAKAR

Title : METHOD OF PURIFYING REDUCED COENZYME Q<sub>10</sub>DECLARATION UNDER RULE 132

Honorable Commissioner of Patents and Trademarks,  
Alexandria, Virginia 22313-1450

Sir:

I, Takahiro Ueda, a citizen of Japan and having  
postal mailing address of 6-31-17-2018, Shioya-cho,  
Tarumi-ku, Kobe-shi, Hyogo 655-0872 JAPAN, declare and say  
that:

March, 2000, I was graduated from Kobe University  
Graduate School of Science and Technology, and received a  
Master Degree in chemistry;

Since April, 2000, I have been employed by Kaneka  
Corporation, and engaged in the works of Research and  
development for fine chemicals in New Products Development  
Team, New Business Development Group, QOL Division;

I am one of the inventors of the above-identified  
application and am familiar with the subject matter  
thereof;

I respectfully submit herewith my exact report;

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Object

The experiment is to determine the solubility of L-ascorbic acid in ethanol.

Experiment

Ethanol (20 g) was added to a 500 mL flask and stirred at 25°C. After 1 hour of stirring, L-ascorbic acid (1 g) was added and stirred at 25°C for 2 hours. The solution was filtered through a membrane filter and a filtrate was analyzed by HPLC.

The solubility of L-ascorbic acid was 0.2 g/100 g EtOH.



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I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Signed this 19<sup>th</sup> day of April, 2010

A handwritten signature in cursive script, reading "Takahiro Ueda", is written over a horizontal line.

Takahiro Ueda



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Partial translation of "Kagaku Binran"

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### 8.8 Solubility

#### c. Solubility of organic compounds in water

(3)

a: Solubility is expressed by the mass of an anhydride and is indicated with the units designated by the following abbreviations.

w: maximum mass (g) of the solute contained in 100 g of the saturated solution (mass %)

Table 8.61

Temperature dependency of solubility of organic compounds in water (see also Table 8.62) (1)

Solute	unit $\theta/^{\circ}\text{C}$	0	10	20	25	30	40	50	60	80	100
		12.1	15.1	18.3	(19.8)	21.3	24.6	27.7	29.7	33.6	36.5
L-ascorbic acid	w										

(End)